REMARKS

Reconsideration of the rejections is respectfully requested.

The term "isolated" has been inserted into claim 30, thereby rendering the issue raised in paragraph 14 of the Office Action moot. This clarification of what clearly is the intended scope of the claimed subject matter is not related to any reason for patentability based on the current record. Claims 59 and 60 are supported on pages 16 and 17 of the specification, among others. These make explicit that the antibodies and fragments of the claims bind in vivo, e.g. in a patient, directly to the ED-B domain of fibronectin, a glycosylated molecule (page 3, lines 17-19; see also claim 37).

Claims 57 and 58, it is respectfully submitted, are not duplicates of claim 30. Claim 57 requires the presence of an antibody; claim 30 does not require an antibody. Whereas an antibody is certainly covered by claim 30, if it is absent but an antibody fragment is present, claim 30 still covers the situation. Thus, claims 30 and 57 are of different scopes. The same analysis applies to claim 58 drawn to the antibody fragment alternative of claim 30. Claim 58 is of a different scope from claim 30 for this analogous reason.

Applicants stand by the Federal Circuit case law discussed, e.g., in the Response of April 10, 2003, which establishes that the examiner's position on claim 47 is incorrect. This claim and the patent specification satisfy all requirements of 35 U.S.C.

Accordingly, under U.S. law, nothing more is required for allowance of claim 47. However, even if the examiner were correct that there had to be some evidence of record that would lead one of skill in the art to believe that the pharmaceutical composition is effective to arrest tumor growth (page 8 of the Office Action of April 13, 2003), such supererogatory evidence is of record.

See, for instance, the two literature references cited at the bottom of page 7 of the Response filed on April 10, 2003. The examiner has not commented at all on these documents. Note especially Santimaria et al. (2003), which establishes in humans that an antibody specific for and binding directly to the ED-B domain of fibronectin is selectively localized in tumors of patients having lung, colorectal and brain cancer. By this selective localization, the antibody enables distinguishing between quiescent and actively growing lesions, without observation of

any side effects. The stated conclusion is that the antibody's ability to target tumors in patients provides the foundation for therapeutic applications. (See the abstract of the paper, for instance.) The earlier Nilsson reference cited in the prior response had shown, in mouse models of three different types of solid tumors (a colon adenocarcinoma, a transformed fibroblast and a teratocarcinoma), tumor eradication (complete at the highest doses, even). Even earlier, also in an animal model, teratocarcinoma was successfully targeted using antibodies exemplified in this application. Neri et al., Nature Biotechnology, vol. 15, Nov. 1997, 1271-1275 (of record). As can be seen, evidence is of record of successful progression of a drug from animal studies to human studies with efficacy being shown. Thus, even if the examiner's position had been correct (not the case, under consistent Federal Circuit case law), the requested evidence is present.

The accompanying translations are of the full texts of the Japanese abstracted documents of record, JP H2-76598 and JP H4-169195. The antibodies which were deposited in conjunction with these Japanese applications have been disposed of because the applicant did not request examination of the applications in the Japanese Patent Office. This information comes from the depository itself. The applications have been withdrawn.

Both of these applications contain insufficient details (e.g., concerning details of screening assay methods for detecting the desired antibodies) to lead a skilled worker necessarily and inevitably to the production of an antibody having the disclosed binding characteristics. *Schering Corp. v. Geneva Pharm., 339 F.3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003)*

Similarly, both applications fail to enable the production of the disclosed type of antibody because undue experimentation would be required, e.g., development of appropriate assay screening methodology for obtaining the desired antibody (if one even were possible), as of the filing date of the instant application. For instance, there are insufficient details given of how the various types of FN are prepared, what their contents or impurities are, what proof existed that the various samples actually did encompass ED-B, or even what proof existed that the samples actually contained FN of any type. Information regarding controls for the Western blots are missing, as is size information. The skilled worker is thus left with a host of critical choices, which together will materially affect the outcome, most notably whether an antibody directly binding to the ED-B domain per se will be obtained, if, indeed, one were possible at all using the

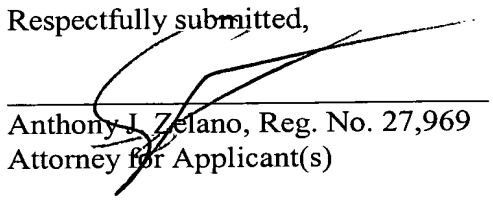
general methodology involved. All of the selections mentioned above, for which no guidance is provided, alone demonstrate that undue experimentation would be required to produce an antibody directly binding to ED-B in accordance with these disclosures, again, if one were producible at all with the general methodology.

Furthermore, it is clear that these documents contain no proof that the asserted types of antibodies were obtained. No evidence of purity of the FN extracts is given, no information on the concentration of the extracts is given, no standard deviations are given for the assay figures, no tests against the ED-B sequences themselves are given, no inhibition experiments are attempted, no histological staining data are attempted, reaction occurs in the figures at least to some extent also with the control FN in the Western blots, etc.

As noted in the background section of the specification, skilled workers have long sought an antibody directed to the ED-B domain, and yet prior to this application, none have achieved one. Note also Peters et al. of record (not long before this application), Cell Adhesion and Communication, 1995, vol. 3, page 67-89, page 85: referring to the "previous difficulty in obtaining antibodies recognizing this segment, as evidenced by the lack of published reports of direct-reacting antibodies since 1987, when the EIIIB segment was first described," by Luciano Zardi, one of the inventors of this application. One would expect that if the Japanese inventors had really successfully obtained antibodies directly binding to ED-B, the deposits would never have been permitted to be destroyed nor the applications abandoned. Further circumstantial evidence along these lines are the facts that these antibodies never again have been mentioned in the literature, as far as could be determined, including in a later paper published by the same group (Fukuda et al, Cancer Research 2002, 62: 5603-5610). It involved research using an antibody binding to the ED-B domain. However, the antibody employed was not any of those mentioned in the two Japanese publications. Instead, the research group raised a new rabbit polyclonal antibody for such purpose, after the instant invention.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Attorney Docket No.: ELLIS-0003

Date: February 14, 2005
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